Outcomes of parenchyma-preserving hepatectomy and right hepatectomy for solitary small colorectal liver metastasis: A LiverMetSurvey study

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Background. *Occasionally, right hepatectomy, rather than parenchyma-preserving hepatectomy, has been performed for solitary small colorectal liver metastasis. The relative oncologic benefits of parenchyma-preserving hepatectomy and right hepatectomy are unclear. This study compared the outcomes of patients with solitary small colorectal liver metastasis in the right liver who underwent parenchyma-preserving hepatectomy and those who underwent right hepatectomy.*

Methods. *The study population consisted of a multicentric cohort of 21,072 patients operated for colorectal liver metastasis between 2000 and 2015 whose data were collected in the LiverMetSurvey registry. Patients with a pathologically confirmed solitary tumor of less than 30 mm in size in the right liver were included. The short- and long-term outcomes of patients who underwent parenchyma-preserving hepatectomy were compared to those of patients who underwent right hepatectomy.*

Results. *Of the 1,720 patients who were eligible for the study, 1,478 (86%) underwent parenchyma-preserving hepatectomy and 242 (14%) underwent right hepatectomy. The parenchyma-preserving hepatectomy group was associated with lower rates of major complications (3% vs 10%; P < .001) and 90-day mortality (1% vs 3%; P = .008). Liver recurrence occurred similarly in both groups (20% vs 22%; P = .39). The 5-year recurrence-free survival and overall survival rates were similar in both groups. However, in patients with liver-only recurrence, repeat hepatectomy was more frequently performed in the parenchyma-preserving hepatectomy group than in the right hepatectomy group (67% vs 31%; P < .001), and the overall 5-year survival rate was significantly higher in the parenchyma-preserving hepatectomy group than in the right hepatectomy group (55% vs 23%; P < .001).*

Conclusion. *Parenchyma-preserving hepatectomy should be considered the standard procedure for solitary small colorectal liver metastasis in the right liver when technically feasible. (Surgery 2017;162:223-32.)*

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Surgical resection offers the best chance for long-term survival in patients with colorectal liver metastases (CLMs).[1] Increasingly aggressive operations, the use of more effective perioperative chemotherapy, and improvements in imaging and patient selection have all contributed to improving the outcomes after resection for CLM.[2] Securing sufficient surgical margins while preserving enough remnant liver parenchyma is the key for safe and effective surgical resection of CLM.[3] Furthermore, it has been well established that repeat resection for recurrent CLM can offer prolonged survival.[4-6]

Occasionally, right hepatectomy (RH), rather than parenchyma-preserving hepatectomy (PH), has been performed for solitary small CLM in the right liver to secure free surgical margins, reducing the risk of liver recurrence. However, to date, it is unclear whether PH increases the positive surgical margins or liver recurrence compared to RH. Furthermore, the oncologic benefit of PH over RH via its leaving enough liver parenchyma to enable repeat resection is also unclear.

Recently, Mise et al reported a single center's experience with PH and non-PH for solitary small CLMs.[7] However, because the policy regarding this clinical situation is usually well designed for only one strategy in each center, a multicenter evaluation was necessary to include both types of strategies.

This study aimed to compare the surgical and long-term outcomes of patients with a solitary small CLM in the right liver who underwent PH and those who underwent RH using the data of a large, recent, multi-institutional, international database. We hypothesized that, in patients with a solitary small CLM in the right liver, PH would be associated with lower morbidity and mortality rates than RH, without increasing positive surgical margins or liver recurrence. Furthermore, we hypothesized that, in patients with liver recurrence, PH would be associated with better survival than RH because preserved liver parenchyma would allow more repeat hepatectomies than RH.

METHODS

Study population. The study population (n = 21,072) consisted of a multicentric cohort of patients operated for CLM between January 2000 and December 2015 and whose data were prospectively registered in the LiverMetSurvey international registry. The LiverMetSurvey (http://www.livermetsurvey.org) is a prospective international database that collects clinical and pathologic data of patients undergoing surgery for CLM. This register currently involves 302 centers across 59 countries. Data are entered using an online questionnaire, which includes demographic and pathologic variables of the primary tumor and of the liver metastases, as well as information concerning the type, duration, and effects of preoperative treatment; the surgical procedure; the timing, location, and treatment of recurrence; and the surgical and long-term outcomes. Data are regularly updated by each center. A data manager performs quality control of the data by automatic control of coherence and by sending personalized information to each contributing center twice a year.

Study design and definitions. Within the global cohort, patients who underwent surgical resection for solitary CLM of less than 30 mm in size in the right liver (segments 5, 6, 7, 8) were eligible for this study. The number and size of CLMs were defined according to the pathologic diagnosis. The following patients were excluded from the study: (1) patients with initially unresectable disease; (2) patients who underwent preoperative portal vein embolization; (3) patients with macroscopically incomplete (R2) resection; and (4) patients showing evidence of concomitant extrahepatic disease.

PH was defined as nonanatomic partial resection or anatomic segmentectomy, bisegmentectomy, and sectionectomy.[8] Major complications were defined as Clavien-Dindo grades III and IV morbidity.[9] Synchronous CLMs were defined as CLMs detected at or before the diagnosis of the primary tumor.[10]

End points and statistical analysis. The primary end points in this study were postoperative major complications as defined above, 90-day mortality, recurrence-free survival (RFS), time to last unresectable recurrence, and overall survival (OS). RFS, time to last unresectable recurrence, and OS rates were calculated from the date of hepatectomy to first disease recurrence, last unresectable recurrence, or death, respectively.[11] The secondary end points of the study were liver recurrence and repeat hepatectomy.

The PH group and RH group were compared using the χ^2 or Fisher exact test for categorical data and the independent-samples t test for continuous data. Survival curves were generated by the Kaplan-Meier method and compared by the log-rank test. To identify predictors of survival among the characteristics of initial hepatectomy in patients with liver-only recurrence, univariable and multivariable analyses were performed using the log-rank test and the Cox proportional hazard model, respectively. A multivariable risk model of

Table I. Comparisons of the PH and RH groups in the overall cohort

Variable	*PH group (n = 1,478)*		*RH group (n = 242)*		P *value*
	No.	*%*	*No.*	*%*	
Patient					
Age, y (mean ± SD)	64.1 ± 11.0		64.0 ± 10.0		.96
Sex: Male	888	60	141	58	.62
Primary tumor					
Location: Rectum	498	34	84	35	.77
T stage: 3/4	1,193	88	176	87	.65
N positive	846	62	126	61	.76
CLM characteristics					
Timing of diagnosis: Synchronous	721	49	121	50	.78
Tumor size, mm (mean ± SD)	19.3 ± 7.6		20.4 ± 8.0		.04
CEA level, ng/mL (mean ± SD)	65.7 ± 303.0		159.7 ± 1,347.6		.06
Perioperative management					
Time period: 2008–2015	1,008	68	162	67	.70
Preoperative CT	1,333	90	225	93	.62
Preoperative MRI	538	36	129	53	<.001
Preoperative PET	527	36	99	41	.12
Preoperative chemotherapy	455	32	84	36	.23
Laparoscopic approach	140	10	5	2	<.001
Postoperative chemotherapy	659	57	193	47	.02
Surgical outcomes					
Blood transfusion	97	8	40	18	<.001
Hospital stay, days (mean ± SD)	10.5 ± 8.1		12.7 ± 12.5		<.001
R0 resection	1,238	94	215	95	.64
Major complications	49	3	24	10	<.001
90-day mortality	11	1	7	3	.008
Long-term outcomes					
Recurrence	529	36	84	35	.77
Liver recurrence	294	20	54	22	.39
Liver-only recurrence	172	12	35	14	.20
Repeat hepatectomy	187	13	18	7	.02

SD, Standard deviation; *CT*, computed tomography; *MRI*, magnetic resonance imaging; *PET*, positron emission tomography.

factors likely to predict survival of patients with liver-only recurrence included variables with $P \leq .10$ on univariable analyses. Factors with $P \leq .05$ were considered predictors of survival of patients with liver-only recurrence. The cut-off values of continuous variables for differentiation between the groups were determined based on receiver-operating characteristic curve analysis. All statistical analyses were performed using JMP version 12.0 (SAS Institute, Inc, Cary, NC).

RESULTS

Study population. Between January 2000 and December 2015, 21,072 patients underwent liver resection for CLM. Of them, 2,060 patients had a histologically solitary, ≤30-mm tumor located in the right liver (Supplemental Fig 1). The following patients were excluded: 73 patients with initially unresectable disease; 50 patients with preoperative portal vein embolization; 76 with R2 resection; and 141 with concomitant extrahepatic disease. Of the 1,720 eligible patients, 1,478 (86%) underwent PH, and 242 (14%) underwent RH.

Comparison of the PH group and the RH group in the overall cohort. Table I shows the patients' characteristics, surgical outcomes, and long-term outcomes of the patients who underwent PH (n = 1,478) or RH (n = 242).

The 3- and 5-year RFS rates were 51% and 43%, respectively, in the PH group and 50% and 41%, respectively, in the RH group (P = .54; Fig 1, *A*). The 3- and 5-year time to last unresectable recurrence rates were 64% and 52%, respectively, in the PH group and 62% and 48%, respectively, in the RH group (P = .17; Fig 1, *B*). After a mean follow-up of 41 months, the 3- and 5-year OS rates

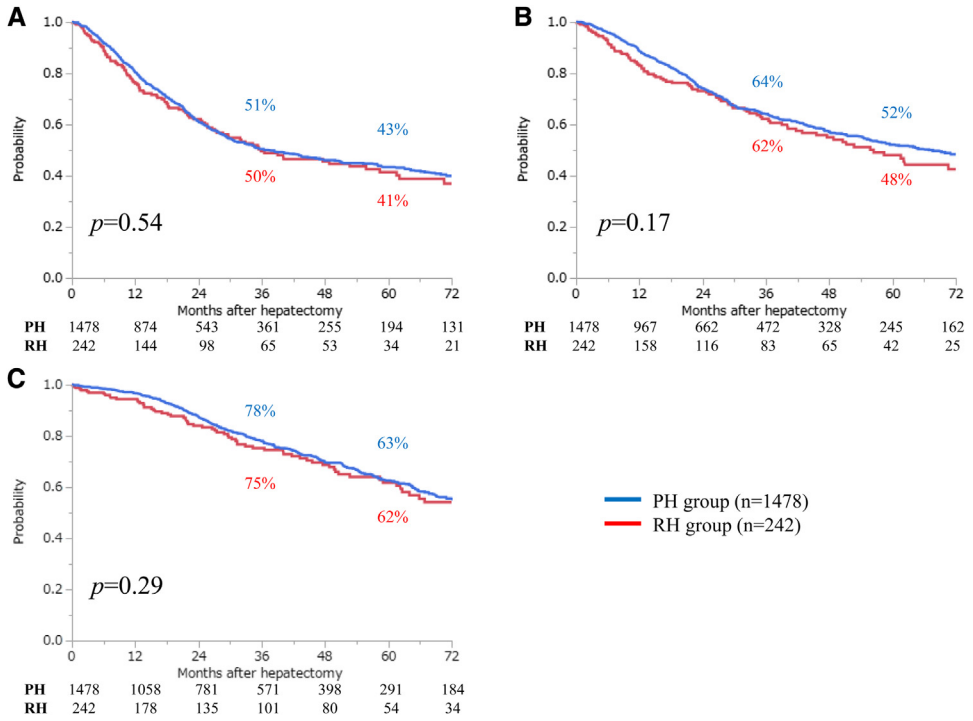

Fig 1. Kaplan-Meier analysis of (*A*) recurrence-free survival (RFS), (*B*) time to last unresectable recurrence, and (*C*) overall survival (OS) of patients who underwent parenchyma-preserving hepatectomy (PH) and those who underwent right hepatectomy (RH) for solitary small colorectal liver metastasis (CLM).

were 78% and 63%, respectively, in the PH group and 75% and 62%, respectively, in the RH group ($P = .29$; Fig 1, *C*).

Comparison of the PH group and the RH group in patients with liver-only recurrence. Table II shows the patients' characteristics, surgical outcomes, and long-term outcomes of patients who developed liver-only recurrence after PH ($n = 172$) or RH ($n = 35$).

In the PH group, 32% of the patients (55/172) had bilateral liver disease recurrence. Of the remaining 68% (117/172) of patients with unilateral liver disease recurrence, 27% (46/172) had recurrence in the right liver (ipsilateral liver) only, whereas 41% (71/172) had recurrence in the left liver (contralateral liver) only (Supplemental Fig 2). Right-liver-only recurrence was less frequent than left-liver-only recurrence in patients with liver-only recurrence after PH (27% vs 41%; $P < .001$). Repeat hepatectomy was performed more frequently in the PH group than in the RH group (67% vs 31%; $P < .001$). In patients with liver-only recurrence after PH ($n = 172$), 110 patients underwent nonanatomical resection as the initial hepatectomy. Of them, 80 patients (80/110; 73%) underwent repeat hepatectomy. On the other hand, in patients with liver-only recurrence after PH ($n = 172$), of 62 patients who underwent anatomic resection as the initial hepatectomy, 35 (35/62; 56%) underwent repeat hepatectomy (Supplemental Fig 3). Repeat hepatectomy was performed more frequently after nonanatomic PH than after anatomic PH or RH.

There was no difference in RFS between the 2 groups ($P = .72$; Fig 2, *A*). However, the 3- and 5-year time to last unresectable recurrence rates were 51% and 35%, respectively, in the PH group and 25% and 9%, respectively, in the RH group ($P = .005$; Fig 2, *B*). Moreover, after a mean follow-up of 35 months, the 3- and 5-year OS rates were 78% and 55%, respectively, in the PH group and 45% and 23%, respectively, in the RH group ($P < .001$; Fig 2, *C*).

Univariable and multivariable analyses of survival of patients with liver-only recurrence. Univariable analyses identified 5 characteristics at initial hepatectomy as being likely to influence OS in patients with liver-only recurrence ($P \leq .10$; Table III): sex, N stage of the primary tumor, tumor size of initial CLM, carcinoembryonic antigen (CEA) levels at hepatectomy, type of procedure, and length of hospital stay. On multivariable analysis, negative nodes of the primary tumor, CEA levels at hepatectomy ≤15 ng/mL, and the PH procedure were identified as independent

Table II. Comparison of the PH and RH groups in patients with liver-only recurrence

Variable	*PH group (n = 172)*		*RH group (n = 35)*		P *value*
	No.	*%*	*No.*	*%*	
Patient					
Age, y (mean ± SD)	63.7 ± 10.9		63.6 ± 10.5		.99
Sex: Male	104	60	20	57	.71
Primary tumor					
Location: Rectum	61	35	14	42	.55
T stage: 3/4	140	89	24	80	.22
N positive	105	66	20	67	1.00
CLM characteristics					
Timing of diagnosis: Synchronous	103	60	13	37	.02
Tumor size, mm (mean ± SD)	17.7 ± 8.0		17.6 ± 7.5		.97
CEA levels, ng/mL (mean ± SD)	41.3 ± 127.4		58.0 ± 110.2		.60
Perioperative management					
Preoperative chemotherapy	58	34	11	33	1.00
Laparoscopic approach	13	8	0	0	.13
Postoperative chemotherapy	68	48	16	53	.69
Surgical outcomes					
Blood transfusion	12	8	10	33	.001
Hospital stay, days					
Median (range)	8 (2–131)		10 (5–127)		
Mean ± SD	10.3 ± 6.1		15.6 ± 21.7		.008
R0 resection	133	90	29	97	.32
Major complications	6	3	2	6	.63
Recurrence characteristics					
Time to recurrence: <12 months	88	51	13	65	.34
Tumor number (mean ± SD)	2.4 ± 2.9		1.4 ± 0.8		.16
Maximum tumor size, mm (mean ± SD)	27.7 ± 23.2		26.0 ± 14.2		.78
Tumor distribution: Bilateral liver	55	32	0	0	
CEA level, ng/mL (mean ± SD)	175.0 ± 621.9		96.4 ± 126.7		.72
Repeat hepatectomy	115	67	11	31	<.001

SD, Standard deviation.

predictors of good prognosis in patients with liver-only recurrence.

DISCUSSION

The present study confirms that, in patients with a solitary small CLM in the right liver, PH is associated with lower postoperative major complication and 90-day mortality rates than RH. Additionally, the present study clearly demonstrates that, in patients with liver-only recurrence after resection for a solitary small CLM, PH is associated with a higher OS rate compared with RH by increasing repeat resection for recurrence. This is the first report to compare PH and RH for solitary small CLMs based on a large, recent, multi-institutional international database.

Mise et al reported a single center's experience with PH and non-PH for solitary small CLMs over a 20-year period.[7] Use of the PH procedure had increased markedly at the MD Anderson Cancer Center over the study period. Furthermore, 3 different procedures, including right hepatectomy, left hepatectomy, and even left lateral sectionectomy, were performed as non-PH procedures. Therefore, it could be argued that the change in the surgical policy with time at a single center and the use of different procedures in the non-PH group might distort the results. Thus, a multi-institutional study was conducted to compare PH and RH for a specific and strictly comparable clinical condition: solitary small CLMs in the right liver.

One of the potential disadvantages of PH compared to RH relates to the higher probability of positive surgical margins affecting the prognosis.[12,13] However, in the current study, positive resection margin rates were similar between the PH group and the RH group. At present, margin width is considered not significantly related to

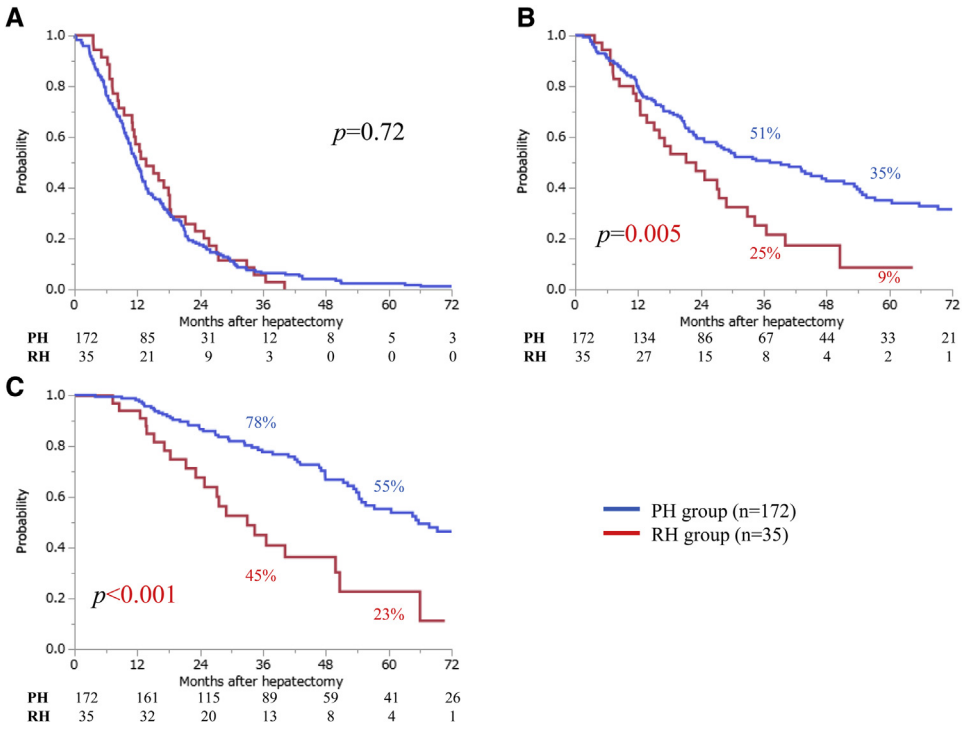

Figure 2. Kaplan-Meier analysis of (*A*) recurrence-free survival (RFS), (*B*) time to last unresectable recurrence, and (*C*) overall survival (OS) of patients with liver-only recurrence who underwent parenchyma-preserving hepatectomy (PH) and those who underwent right hepatectomy (RH) for a solitary small colorectal liver metastasis (CLM).

survival after resection for CLM,[14] and a 1-mm surgical margin could be curative.[15] More recently, it has been reported that even R1 resection, when R0 resection is not possible, might be acceptable in selected patients.[16-18] Meanwhile, the current study showed that the PH procedure, rather than margin status, was an independent prognostic factor in patients with liver-only recurrence. These findings indicate that preserving liver parenchyma has, in practice, more impact on survival than margin width or margin status in patients with a solitary small CLM. Therefore, RH should not be performed for a solitary small CLM only because of a predicted close resection margin.

RH could be considered to decrease the risk of liver recurrence compared to PH, due to wide removal of the at-risk liver parenchyma in which liver metastases could seed.[7] However, the liver recurrence rate was similar between the 2 groups in this study. Furthermore, PH did not increase ipsilateral liver recurrence, as previously reported.[19] These comparable liver recurrence rates after PH and after RH may be attributed to the induction of proliferation of micrometastases, as well as liver regeneration, by upregulating the expression of cytokines and growth factors after a major hepatectomy.[20,21] Thus, despite the benefit of RH in removing the liver parenchyma at high risk of future liver metastases, regenerative growth factors after RH may induce liver parenchymal regeneration and tumor recurrence at the same time. Therefore, RH is not necessary or is useless in preventing liver recurrence after resection for a solitary small CLM.

Some patients may even benefit from repeat hepatectomy in the face of liver recurrence; thus, the preservation of liver parenchyma at the time of initial hepatectomy is potentially valuable.[22] Theoretically, patients undergoing PH, with the resultant preservation of the parenchyma, are more likely to have sufficient functional hepatic volume to allow for aggressive repeat resections when curative resection is possible. However, the relationships between the remnant liver volume after resection for CLM and salvageability for liver recurrence have not been clearly demonstrated. Thus, a subanalysis of patients with liver-only recurrence after resection for a solitary small CLM was conducted. In the present study, although there were no differences in the incidence and characteristics of recurrent CLM between the 2 groups, repeat hepatectomy could be performed more frequently after PH than after RH, and, in addition, time to last unresectable

Table III. Univariable and multivariable analyses of survival of patients with liver-only recurrence

Variable	n	*5-y OS (%)*	*Univariable* P	*Multivariable* P	*RR*	*95% CI*
Patient						
Age, y						
≤65	115	49	.69			
>65	92	51				
Sex						
Male	124	59	.02	.07	1.77	0.96–3.27
Female	83	37				
Primary tumor						
Location						
Rectum	75	51	.88			
Colon	130	49				
T stage						
3/4	164	50	.91			
1/2	23	47				
N stage						
1/2	125	42	.02	.04	0.47	0.23–0.95
0	65	64				
CLM characteristics						
Timing of diagnosis						
Synchronous	116	49	.71			
Metachronous	90	52				
Tumor size, mm						
≤20	136	54	.11			
>20	71	42				
CEA levels, ng/mL						
≤15	76	57	.01	.05	1.85	1.01–3.37
>15	51	36				
Hepatectomy characteristics						
Preoperative chemotherapy						
+	69	45	.96			
−	133	54				
Type of approach						
Laparoscopic	13	0	.12			
Open	192	49				
Type of procedure						
PH	172	55	<.001	.001	3.70	1.77–7.72
RH	35	23				
Blood transfusion						
+	22	44	.24			
−	155	54				
Hospital stay, days						
≤14	163	53	.004	.10	1.82	0.89–3.72
>14	33	37				
Margin status						
R0	162	53	.99			
R1	16	43				
Major complications						
+	8	56	.14			
−	199	50				
Postoperative chemotherapy						
+	84	49	.79			
-	89	57				

RR, Risk ratio; *CI*, confidence interval.

Table IV. The number of patients with solitary CLM according to tumor size in the LiverMetSurvey

	PH group (n =*1,883*)		*RH group* (n = *368*)		
	No.	*%*	*No.*	*%*	P *value*
Tumor size (mm)					
≤20	861	46	126	34	<.001
21–30	617	33	116	32	.64
31–40	405	22	126	34	<.001

recurrence was significantly longer after PH than after RH. On multivariable analysis, PH as the initial hepatectomy procedure was an independent prognostic factor in patients with liver-only recurrence. These findings indicate that the remnant liver volume after initial hepatectomy might correlate proportionally with salvageability for liver recurrence and survival of patients with CLM. This might be supported by the fact that repeat hepatectomy was performed more frequently after nonanatomic PH than after anatomic PH or RH in patients with liver-only recurrence. Therefore, it could be considered that, in patients with a solitary small CLM in the right liver, PH increases the chance of performing repeat resection for liver recurrence and, if so, leads to prolonged survival compared to RH.

The pathologic number and size of CLMs were used for selecting patients eligible for this study. Because techniques and quality of imaging studies might differ greatly in centers across the world, we decided to base our analysis on pathologic diagnosis, which seems more reproducible.

Tumor size is one of the most important factors in selecting PH or RH. An analysis of the number of patients with solitary CLM who underwent PH or RH according to tumor size (≤20 mm, 21–30 mm, 31–40 mm) in the LiverMetSurvey showed that, for CLM of 31–40 mm in size, PH was performed less frequently than RH ($P < .001$; Table IV). Therefore, the study was restricted only to patients with a solitary CLM of <30 mm in size to exclude cases for which RH was inevitable to remove a large tumor.

It has been reported that the laparoscopic approach yields short- and long-term outcomes similar to those for the open approach for CLM.[23,24] Therefore, although the laparoscopic approach was more frequently performed in the PH group than in the RH group, the 2 groups in this study remained comparable in terms of outcomes.

In the overall cohort, long-term outcomes were similar between the PH group and the RH group. Because CLM represents a systemic disease, the incidence of recurrence is as high as 75%, even after curative resection.[11] In the current study, despite selecting the patients with the most favorable tumor biology among the CLM patients (solitary, ≤30 mm in size), the overall recurrence rate was about 35% in both groups. For this reason, the long-term outcomes of the patients who underwent PH and RH might be similar in the overall cohort. However, the development of a first relapse after initial hepatectomy does not mean definitive surgical failure or noncurability because repeat resection for recurrent disease has been accepted as providing a survival benefit and another chance for cure.[11] Therefore, it is meaningful that the subgroup analysis of the patients with liver-only recurrence showed that PH was associated with a higher overall survival rate than RH because preserved liver parenchyma allowed more repeat hepatectomies than RH.

Finally, an important issue to consider is the risk of the operative procedure. Obviously, PH has less morbidity and mortality risk than RH. This, in view of the absence of any benefit provided by RH, clearly increases the risk–benefit ratio of RH compared to PH.

This study has several limitations. The first limitation of this study is its retrospective nature and the long study period. Second, pathologic tumor size was smaller and postoperative chemotherapy was performed more frequently in the PH group than in the RH group. The propensity score method enables us to obtain 2 groups that are well balanced for prognostic factors.[25,26] However, including posttreatment variables as factors to calculate propensity scores is not recommended.[27] Therefore, applying propensity score methods to match the pathologic tumor size and postoperative chemotherapy between the 2 groups was not appropriate. Third, there were no data about

vascular connection of the resected metastases in the LiverMetSurvey. Thus, it was not possible to clearly identify patients who underwent RH but would have been technically suitable candidates for PH; however, the patients with initially unresectable disease due to vascular proximity were excluded from this study. Thus, the potential influence of this issue on the results was probably limited. Fourth is the study's multicentric nature, with a variability of policy between centers in selecting the operative procedure. However, a comparative study of 2 different procedures might be difficult to conduct at a single center due to changes of surgical philosophy over time.[28] Therefore, the present approach still provides a useful means of evaluating treatment methods for solitary small CLMs more precisely than was possible with conventional, retrospective, single-center studies.

In conclusion, this recent, large, multi-institutional study demonstrated that, in patients with a solitary small CLM in the right liver, PH was associated with lower major complication and 90-day mortality rates than RH, without increasing positive surgical margins or liver recurrence. In patients with liver-only recurrence, PH was associated with a higher OS rate than after RH because preserved liver parenchyma allowed more repeat hepatectomies than RH. Therefore, in patients with a solitary small CLM in the right liver, PH, rather than RH, should be considered the standard procedure when technically feasible.

SUPPLEMENTARY DATA

Supplementary data related to this article can be found online at http://dx.doi.org/10.1016/j.surg.2017.02.012

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